SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

| REPORT DOCUMENTATION PAGE | READ INSTRUCTIONS BEFORE COMPLETING FORM |
|---|---|
| 1. REPORT NUMBER | 2. GOVT ACCESSION NO. AD-A099143 | 3. RECIPIENT'S CATALOG NUMBER |
| 4. TITLE (and Subtitle) Water and electrolyte exchange during exposure to cold, altitude and combined cold and altitude. | 5. TYPE OF REPORT & PERIOD COVERED Final 1975-1981 |
| | 6. PERFORMING ORG. REPORT NUMBER |
| 7. AUTHOR(s) Melvin J. Fregly, Ph.D. | 8. CONTRACT OR GRANT NUMBER(s) N00014-75-C-0199 |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS University of Florida, College of Medicine, Gainesville, Florida 32610 | 10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS |
| 11. CONTROLLING OFFICE NAME AND ADDRESS Physiology Program (Code 441), Office of Naval Research, 800 N. Quincy Street, Arlington, VA 22217 | 12. REPORT DATE 28 April 1981 |
| | 13. NUMBER OF PAGES 10 |
| 14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) Office of Naval Research, Resident Representative, Georgia Institute of Technology, 214 O'Keefe Building, Atlanta, GA 30332 | 15. SECURITY CLASS. (of this report) Unclassified |
| | 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE |
| 16. DISTRIBUTION STATEMENT (of this Report) 441:LML:716:abc 80u441-200, dated 10 July 1980 | DISTRIBUTION STATEMENT A Approved for public release; Distribution Unlimited |
| 17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report) | |
| 18. SUPPLEMENTARY NOTES | |
| 19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Thermogenic Drinking; Cold-Induced Dehydration; Cold Adaptation: Beta-Adrenergic Responsiveness; Plasma Renin Activity; Altitude-Induced Dehydration: Water Exchange; Adaptation To Altitude; Hypoxia | |
| 20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Exposure of rats to air at 5° C. for 1 to 12 days is accompanied by a relative dehydration in spite of the continued presence of water. Dehydration was manifested by: (a) a reduction in the ratio of water/food ingested; (b) an increase in the ratio of urine excreted/water ingested; (c) an increased evaporative water loss; (d) an increased serum osmolality and chloride concentration and (c) a striking thirst and ingestion of water following transfer from cold to air at 26° C. Drinking began within 15 minutes and lasted approximately | |

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Unclassified

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1 hour. Thermogenic drinking persisted for at least 120 days of exposure to cold. It was not thwarted by preventing access to water for either 1 or 2 hours following transfer to warm air, but either intragastric or intraperitoneal administration of a water load equal to 3% of body weight inhibited water intake following transfer. These characteristics of thermogenic drinking are similar to those observed following 24 hours of dehydration at 26° C. and also suggest that the cold-exposed rat is dehydrated relative to controls. These results suggest that osmoreceptors may play a role in the induction of thermogenic drinking. However, angiotensin II receptors may also play a role. Thermogenic drinking was inhibited by beta-2, but not beta-1-adrenergic antagonists as well as by captopril, an inhibitor of the conversion of angiotensin I to angiotensin II. This suggests that an additional component involved in thermogenic drinking is the angiotensin II receptor. The extent to which thermogenic drinking is mediated by each type of receptor is unknown and will require additional studies.

Rats exposed chronically to cold air have an increased responsiveness to beta-adrenergic stimulation as exemplified by a greater increase in heart rate and tail skin temperature and a greater decrease in peripheral resistance following administration of isoproterenol. No effect of the alpha-adrenergic agonist, phenylephrine, on tail skin temperature of either control or cold-acclimated rats was observed. Further, the tension developed by aortic smooth muscle rings of CA and control rats during stimulation of alpha-adrenergic receptors by norepinephrine is reduced significantly in the CA group. However, acclimation to cold air did not alter responsiveness of aortic rings to KCl. This suggests an unchanged contractile mechanism in aortic smooth muscle from CA rats but a reduced responsiveness either at the level of the alpha-adrenergic receptors or at a site immediately beyond. These results also suggest that beta-adrenergic receptors may play a dominant role in acclimation to cold in the laboratory rat. Since an increase in the rate of secretion of thyroid hormones occurs during exposure to cold, it is possible that thyroid hormones may play an important role in the increased responsiveness to beta-adrenergic stimulation that accompanies cold acclimation in the laboratory rat. Studies from this laboratory have shown that reduction in thyroid activity reduces, while increases in thyroid activity increases, responsiveness to beta-adrenergic stimulation.

Rats exposed chronically to hypoxia (12% oxygen in nitrogen) became dehydrated. They decreased their water intake below prehypoxic control levels during the first 2 weeks of exposure but gradually returned water intake to control level by the 4th week of exposure. In contrast, daily urinary output was uninfluenced by hypoxia. Comparison of the relation between urinary flow rate and total solute excretion rate revealed for experimental rats a smaller solute excretion rate at a given urinary flow rate than for controls. In addition, rats exposed to hypoxia were unable to concentrate their urine to the level of control rats after 24 hours of dehydration. Serum osmolality and specific gravity were significantly higher for experimental rats. In addition, hypoxia-treated rats drank large amounts of water immediately after removal from hypoxia. These results suggest that chronic exposure to hypoxia also induced a state of dehydration in rats, possibly as a result either of an attenuated response to, or reduced production of, endogenous antidiuretic hormone. The failure of spontaneous water intake to maintain normal serum osmolality during exposure to hypoxia cannot be explained nor is there an adequate explanation for the persistent increase in water intake after removal from the hypoxic environment. These observations will require additional studies.

FINAL REPORT

# WATER AND ELECTROLYTE EXCHANGE DURING EXPOSURE TO COLD, ALTITUDE AND COMBINED COLD AND ALTITUDE

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CONTRACT N00014-75-C-0199 WITH THE OFFICE OF NAVAL RESEARCH

PERIOD COVERED: 1975 TO 1981

Dehydration is reported to occur in man exposed to cold. Rats appear to respond in an analogous fashion in that they become dehydrated when exposed to air at 5°C. for 1 to 12 days in spite of the continued presence of water. Dehydration was manifested by: (a) a reduction in the ratio of water/food ingested during cold exposure; (b) a two fold increase in evaporative water loss; (c) an increased serum osmolality and chloride concentration; and (d) a striking thirst following removal from cold air. Using the rat as a model of man, studies have been carried out to determine whether cold-induced dehydration is related to an attenuation of thirst mechanisms and drinking or to an attenuation of the ability to conserve water on the part of the kidneys, or both.

After as little as 6 hours of exposure to air at 5°C., drinking was induced in rats following transfer from air at 5°C. to air at 26°C. Drinking began within 15 minutes after transfer from the cold and lasted approximately 1 hour. The stimulus for initiation of drinking was related not only to dehydration but also to the temperature change resulting from the transfer, since an ambient temperature difference of 10 Centigrade degrees or more was required to initiate a drinking response after transfer from air at 5°C. Post-cold exposure drinking was not thwarted by preventing access to water for either 1 or 2 hours following transfer to warm air, but either intragastric or intraperitoneal administration of a water load equal to 3% of body weight inhibited water intake following transfer. The characteristics of the drinking response following transfer from 5 to 26°C. were similar to those observed following 24 hours of dehydration at 26°C. Hence, these observations also suggest that the cold-exposed rat is relatively dehydrated compared to rats maintained in air at 26°C.

When rats were removed from cold and immediately offered water at either 5, 10, 15, 20, 25, 30, 35, or 40°C. to drink, both cold-treated and control rats ingested increasing volumes of water with increasing water temperature during a 1 hour test period. However, cold-treated rats ingested significantly more water than controls at any temperature offered. Cold-induced dehydration appeared mainly to exaggerate rate of water intake at a given water temperature. A surprising observation was that both cold-treated and control rats ingested maximal amounts of water when the water temperature was approximately body temperature. This has uncovered the possibility that water temperature may be an important factor in the rate at which rehydration occurs in man.

Spontaneous water intake of cold-exposed rats did not increase during cold exposure in spite of an increased food intake, urine output, evaporative water loss, and serum osmolality. Since water intake increased immediately after an abrupt transfer of rats from the cold to a warm environment, the possibility existed that the abrupt change in skin temperature may have been the stimulus for drinking. To test this hypothesis, room temperature was rewarmed slowly at rates of 0.5 and 1.0°C./minute and thermogenic drink measured after room temperature had equilibrated at 26°C. for 20 minutes. Cold-treated rats still ingested significantly more water than controls during the first hour water was available. This suggests that rate of warming of the skin is not a major factor responsible for induction of thermogenic drinking in cold-treated rats.

A possibility existed that the temperature of the water available to rats during exposure to cold might be a factor in the thermogenic drink. By means of a specially constructed water container, rats were offered water at 5, 15, 25 and 35°C. during exposure to cold. Availability of water at temperatures higher

than ambient (5°C.) failed both to affect the ratio of water to food intake during exposure to cold air and to influence the thermogenic (post-cold exposure) drinking response of rats which characteristically occurs immediately after removal from cold air. Thus, availability of warm water during exposure to cold appeared to have no influence on cold-induced dehydration in rats.

Exposure of rats to air at 5°C. increases urinary flow rate significantly above that of controls maintained at 26°C. The greater urinary flow rate was reduced both by administration of pitressin (either 200 or 500 mU/rat) and a 24 hour period of dehydration, but not to the level of controls maintained at 26°C. Urinary osmolality was similarly affected by cold exposure; i.e. cold-exposed rats were unable to increase their urinary osmolality to the level of the control group following either administration of pitressin or dehydration. In addition, urinary flow rate for a given urinary osmolality was greater for cold treated rats than for controls. These observations suggest that exposure to cold is accompanied by an altered response to antidiuretic hormone in the rat but they do not eliminate the possibility that less antidiuretic hormone may be produced by cold-exposed rats. Studies of others have shown that elevated blood levels of either glucocorticoid hormones (cortisone, hydrocortisone) or norepinephrine inhibit the antidiuretic effect of administered pitressin. These may contribute to the reduced ability of the cold-exposed rat to concentrate its urine since both of these hormones are secreted in excess during chronic exposure to cold.

Several types of receptors are now known to mediate thirst and drinking; these are osmoreceptors and angiotensin II receptors. Both sets of receptors are located in the brain and outside of the blood-brain barrier in the subformical organ and the organium vasculosum of the lamina terminalis. The studies described above suggest that osmoreceptors are involved in drinking induced after removal from cold, i.e. thermogenic drinking, since cold-exposed rats appear to be dehydrated and serum osmolality is increased. The question as to wheither angiotensin II receptors may also be involved has been considered.

Recently, it has been shown that thirst can be induced under conditions which include extracellular hypovolemia, hyponatremia and intracellular hypervolemia. A chronic sodium deficiency will induce these changes and is accompanied by thirst and an increased secretion by the renin-angiotensin system. It is known that angiotensin II, administered into the brain in the region of the subfornical organ and the preoptic area, will elicit thirst. If administered peripherally at somewhat higher doses, water intake can also be stimulated. Peripheral angiotensin II is believed to cross the blood-brain barrier in the region of the circumventricular organ. It is now well known that administration of the β-adrenergic agonist, isoproterenol, stimulates the release of renin from juxtaglomerular cells of the kidney. Renin, after combining with renin substrate in blood, forms angiotensin I, a decapeptide, which is converted to angiotensin II, an octapeptide, by a converting enzyme located mainly in the vascular beds of the lung.

Additional studies were carried out to determine wheither the renin-angiotensin system might also play a role in thermogenic drinking. One important factor initiating renin release is the β-adrenergic system. Isoproterenol, the β-adrenergic agonist, is a potent dipsogen, as are renin and angiotensin II. A possibility existed that at least one factor in the initiation of thermogenic drinking might be the increased rate of secretion of catecholamines induced by cold exposure. To assess this possibility, d,l-propranolol, a β-adrenergic

antagonist, was tested to determine its effect on thermogenic drinking. d,l-Propranolol, administered at 6 mg/kg b.w. 0.5 hour prior to removal from cold significantly inhibited thermogenic drinking in cold-treated rats. This dose of propranolol did not affect significantly the drinking response of control rats. Propranolol-treated, cold-adapted rats drank about one-third the amount of water ingested by untreated, cold-adapted rats. However, propranolol failed to reduce water intake of the cold-adapted rats to that of the untreated control group.

To determine whether the effect of d,l-propranolol might be related to its membrane-stabilizing and central nervous effects, d-propranolol (6 mg/kg) was also used. This isomer contains little β-adrenergic antagonistic activity but has the membrane-stabilizing and central nervous characteristics of the l-isomer. d-Propranolol failed to influence the thermogenic drink.

Since β-adrenergic receptors can be subdivided further into $\beta_1$ and $\beta_2$ types, additional studies were carried out to characterize further the receptor type concerned with thermogenic drinking. Administration of proctolol, a $\beta_1$-adrenergic antagonist, at either 50 or 150 mg/kg b.w. 0.5 hour prior to removal from cold had no significant effect on thermogenic drink. However, administration of the $\beta_2$-adrenergic antagonist, butoxamine, at 35 mg/kg 0.5 hour prior to removal from cold reduced significantly the thermogenic drink.

These studies showed that thermogenic drinking following transfer of rats from 5 to 26°C. can be inhibited by prior administration of a $\beta_2$-adrenergic antagonist. The inhibition does not appear to be due to central nervous effects of the drug. Thus, it appears that the thermogenic drinking response arises, in part at least, as a result of stimulation of $\beta_2$-adrenergic receptors during transfer of rats from a cold to a warm environment. Since $\beta_2$-adrenergic receptors also appear to mediate the release of renin from the juxtaglomerular cells of the kidney, it seemed possible that the renin-angiotensin system might play a role in the thermogenic drinking response. To test this possibility, plasma renin activity was measured in control rats maintained at 26°C., in cold-adapted rats maintained at 5°C., and in treated rats 15 minutes after removal from 5 to 26°C. The results of this study revealed that cold exposure per se did not affect plasma renin activity significantly. However, within 15 minutes after removal from cold, plasma renin activity increased four-fold. An additional study showed that administration of propranolol prior to removal from cold prevented the increase in plasma renin activity. This indicates that removal from cold is associated with an increase in the formation of angiotensin II which could account, in part at least, for the thermogenic drink.

To test further this possibility, the angiotensin I converting enzyme inhibitor, captopril, was administered i.p. to rats 15 minutes prior to transfer from the cold to a neutral environment. At the same time, other cold-treated rats were administered an equal volume of the vehicle used to dissolved captopril. This group was also transfered from the cold to a neutral environment. Two additional groups, not previously exposed to cold, were also used. The first served as the control group, while the second received the same dose of captopril as that of the cold-treated group. Water intakes of all rats were measured at 0.5, 1.0 and 2.0 hours after removal from cold. A series of studies using 10, 25, 35 and 50 mg captopril/kg body weight was conducted. The

results of these studies revealed a graded reduction in the thermogenic drinking response with graded increases in the dose of captopril administered prior to transfer from the cold to a thermoneutral environment.

The results of this study suggest that thermogenic drinking may be mediated, in part at least, by activation of the β-adrenergic system which induces an increase in plasma renin activity and the formation of angiotensin II. The latter is the dipsogenic agent responsible for the induction of drinking. Support for a role of angiotensin II in thermogenic drinking is obtained from the elevated plamsa renin activity of rats removed from the cold to a neutral environment. This coincides with the time for induction of a thermogenic drinking response. Additional evidence that angiotensin II may be important in the thermogenic drinking response is the dose-dependent blocking effect of captopril which inhibits conversion of angiotensin I to angiotensin II.

Experimental results to date suggest that thermogenic drinking is mediated both by osmoreceptors and angiotensin II receptors. Present results do not show the extent to which each may contribute to the thermogenic drink. Thus, a possibility exists that the thermogenic drinking response of the cold-treated rat is of sufficient physiological importance to have redundancy in the mechanisms initiating it.

The metabolic responsiveness of cold-adapted rats to β-adrenergic stimulation was tested by way of increases in tail skin temperature and heart rate following administration of graded doses of isoproterenol. Cold-adapted rats removed from cold for 24 hours prior to the study responded at each dose of isoproterenol with greater increases in tail skin temperature and heart rate than non-adapted controls. The responsiveness of α-adrenergic receptors of rings of aortic smooth muscle of cold-adapted rats was tested in vitro during receptor stimulation by norepinephrine and membrane depolarization by KCl. The tension developed by aortic segments of cold-adapted rats following graded doses of norepinephrine was significantly less than controls but was not altered following administration of KCl. This suggests an unchanged contratile mechanism in aortic smooth muscle of cold adapted rats but a reduced responsiveness either at the level of the α-adrenoreceptors or at a site immediately beyond. Thus, the cold-adapted rat may have increased responsiveness to β-adrenergic stimulation but reduced responsiveness to α-adrenergic stimulation.

The tail serves the important function of thermoregulation in rats. When the body of the rat is threatened with overheating, tail skin temperature increases as a mechanism for dissipation of the excess heat produced. A direct effect of rising blood levels of catecholamines on tail blood vessels of cold-exposed rats coupled with an increasing responsiveness of β-adrenergic receptors would be expected to increase heat loss under conditions in which heat conservation should be maximized to maintained body temperature. Studies were directd to the question whether the increase in tail skin temperature following administration of isoproterenol was the result of a direct action of the drug on tail vasculature or an indirect effect resulting from the increase in metabolic rate and heat production induced by isoproterenol. The results of the study showed that metabolic rate increases and is maximal at the time tail skin

temperature begins to increase following administration of isoproterenol. This would suggest that the increase in tail skin temperature is an indirect effect and serves the function of dissipating the excess heat resulting from the increase in metabolic rate induced by isoproterenol.

Maintenance of a constant body temperature during exposure to cold air involves a significant hormonal interaction. The hormones most commonly studied in this regard are thyroid hormones and catecholamines. Several studies have been carried out to assess their interaction. Thus, hypothyroidism appears to be accompanied by a reduced β-adrenergic responsiveness as assessed by changes in tail skin temperature, water intake, heart rate, and plasma glucose concentration after administration of isoproterenol. Since administration of thyroxine maintained the responses of hypothyroid rats at control levels, it appears that thyroxine plays an important permissive role under these conditions. Since chronic exposure to cold air is well known to increase the secretory activity of the thyroid gland, it is possible that the increased β-adrenergic responsiveness of cold-adapted rats may be related to the increased activity of their thyroid glands. Additional studies are needed to test this possibility.

To assess the changes in β-adrenergic responsiveness of rats during chronic exposure to cold, rats that had been exposed to cold (6 C) for 10, 15, and 25 days were administered isoproterenol acutely (50 ug/kg, s.c.). The increases in tail and colonic temperatures accompanying treatment with isoproterenol were significantly greater in cold-acclimated than control rats. Administration of isoproterenol (8 ug/kg, s.c.) to cold-acclimated rats (1,3, 5, 7, 14, and 28 days) increased heart rates above that of controls. However, resting, unstimulated heart rates of cold-acclimated rats were also increased above that of controls after 1, 3, 5, and 7 days of cold exposure but were not different from controls after 14 and 28 days. Cold exposure also led to time-dependent increases in the weights of heart, adrenals and interscapular brown fat. Thus, chronic exposure of rats to cold is accompanied by an increase in responsiveness of both heart rate and tail skin and colonic temperatures to β-adrenergic stimulation. The results also suggest that increases in responsiveness to a β-adrenergic agonist may not occur at the same time for different β-adrenergic-mediated metabolic and cardiovascular responses in cold-acclimated rats.

The effect of chronic administration of isoproterenol on isoproterenol-induced thirst, isoproterenol-induced changes in heart rate and selected organ weights of male rats was studied. Administration of 25 ug isoproterenol/kg, s.c. in saline daily for 10 days was accompanied by a significant attenuation of the characteristic increase in water intake following acute administration of isoproterenol (25 ug/kg, s.c.) on the 11th day. Administration of 25 ug isoproterenol/kg, s.c. every second, third, or fourth day for 10 days was without significant effect on water intake following isoproterenol (25 ug/kg) on the 11th day. Chronic treatment with this low dose of isoproterenol for 10 days was also accompanied by a significant increase in the ratio of heart weight/body weight but no significant changes in the ratio of kidney, adrenal, thyroid, spleen or interscapular brown fat to body weight.

Thus, daily administration of the β-adrenergic agonist, isoproterenol, for 10 days can alter $\beta_1$- (heart rate) and $\beta_2$- (thirst) mediated responses in divergent ways. In addition, the results suggest that tests of β-adrenergic responsiveness must be assessed in terms of the frequency of administration of the angonist.

An *in vitro* model was employed to evaluate the effect of cold-acclimation on peripheral outer ring deiodination of thyroxine ($T_4$) to triiodothyronine ($T_3$) by 9,000 x g supernatants of fresh liver homogenates. Hepatic $T_3$ generation from $T_4$ in male rats exposed to 4°C. for 12 weeks was 41 and 24% higher than control after 30 and 60 minute incubation periods, respectively. This was associated with a 49% increase in serum $T_3$ concentration in the cold-acclimated rats, whereas serum $T_4$ concentration did not differ from control. Thus, hepatic deiodination of $T_4$ appears to serve as an important source for production of $T_3$ during cold acclimation. It is suggested that the increased β-adrenergic activity observed previously in cold-acclimated rats stimulates this change.

While studies related to thermogenic drinking were being carried out, the observation of another experimental situation which induces a large, previously unreported "thirst" in rats was made. Exposure for 26 days to an atmosphere containing either 11.0 or 12.5% oxygen increased their spontaneous water intake after return to control environment (20.9% oxygen). The increased water intake persisted for 2 (12.5%) to 11 (11.0%) days. Other rats exposed to an atmosphere containing 12.0% oxygen decreased their water intake below prehypoxic control levels during the first 2 weeks of exposure but gradually returned water intake to control level by the 4th week of hypoxia. In contrast, daily urinary output was uninfluenced by hypoxia. Comparison of the relationship between urinary flow rate (ml/24 hours) and total solute excretion rate (milliosmols/24 hours) revealed for experimental rats a smaller solute excretion rate at a given urinary flow rate than for controls. In addition, rats exposed to hypoxia were unable to concentrate their urine to the level of control rats after 24 hours of dehydration. Measurement of serum osmolality and specific gravity during the 32nd day of exposure to hypoxia revealed higher values for experimental rats. After removal from hypoxia, experimental rats ingested more water than controls within one hour. The greater drinking response persisted for 4 to 5 days post-hypoxia. These results suggest that chronic exposure to hypoxia also induces a state of dehydration in rats possibly as a result either of an attenuated response to, or reduced production of, endogenous antidiuretic hormone. The failure of spontaneous water intake to maintain normal serum osmolality during exposure to hypoxia cannot be explained nor is there presently and adequate explanation of the persistent increase in water intake after removal from the hypoxic environment.

The effect of combined cold (5°C. air) and hypoxia (12% oxygen in nitrogen) on water exchange was also studied using 24 male rats divided into 4 equal groups. During a 5 day control period, distilled water and food intakes, urine output, and body weight were measured daily. At the end of this time, Group 1 served as control, while Group 2 was exposed to 12% oxygen; Group 3 to air at 5°C., and Group 4 to both. All measurements continued during the first 3 weeks of the experimental period. Regression analysis of water intake on urine output revealed that at a given water intake, all 3 treated groups excreted significantly more urine than control.

No significant differences occurred among treated groups. Serum osmolalities of all 3 treated groups, measured at the end of the 48 day treatment period, were elevated above the level of the control group. All treated groups also manifested a thirst immediately following return to control environment. Thus, the 3 treated groups appeared to be dehydrated relative to the control group. The results further suggest that the effect of combined cold and hypoxia on water exchange is not a summation of that occurring separately during cold and hypoxia. The factors inducing dehydration in cold and hypoxia are apparently related to increased evaporative water loss and to alterations in thirst and renal mechanisms.

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